

## **REMARKS**

### **Status of the Claims**

Prior to this amendment, claims 14, 20-23 and 34-39 were pending. Claims 23 and 34-36 were withdrawn by the Examiner as being drawn to nonelected subject matter. Claims 14, 20-22 and 37-39 were examined and rejected. Claims 14 and 37 are herein amended to clarify the invention. Support for the amendment may be found, for example, in the specification as filed at page 16, lines 12-21, page 23, line 30 through page 24, line 31, and page 26, line 12. No new matter has been added. Upon entry of this amendment, claims 14, 20-23 and 34-39 will be pending. Entry of the amendment and reconsideration on the merits are respectfully requested.

### **Rejection under 35 U.S.C. § 112, First Paragraph**

Claims 14 and 20-22 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for treating neuropathic pain with N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide, allegedly does not reasonably provide enablement for the prophylaxis of neuropathy and related disorder.

Claim 14 has been amended to delete the term “prophylaxis,” thereby rendering this rejection moot. Accordingly, Applicant respectfully submits that the rejection may be withdrawn.

### **Rejection under 35 U.S.C. § 102**

Claims 14 and 20 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Walker *et al.* (*Pain* 1999, 83:509-516, “Walker”). Walker allegedly teaches that asimadoline is effective for the treatment of neuropathic pain, which is a major symptom of neuropathy. Walker allegedly further teaches intraplantar injection into the nerve-injured paw of rat with neuropathic pain. As such, the Office concludes that Walker anticipates all the limitations of the instant claims 14 and 20.

Applicant respectfully traverses this rejection for the reasons set forth below.

The legal standard for anticipation under 35 U.S.C. § 102 is one of strict identity. *Trintec Industries, Inc. v. Top-U.S.A. Corp.*, 63 U.S.P.Q.2d 1597 (Fed. Cir. 2002). To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention. *In re Paulson*, 30 F.3d 1475, 1478-79, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994) (citing *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990)). “A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131.

Claim 14 as amended is directed to the systemic treatment of neuropathy with N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide or a derivative, solvate, salt or stereoisomer thereof. Walker discloses the administration of asimadoline in chronic constriction injury (CCI) neuropathic rats. Low-dose intraplantar (but not systemic) administration of asimadoline produced an anti-nociception effect in the rats. *See* pages 511-512, Section 3.3, stating “intravenous . . . administration of asimadoline produced no change in nociceptive thresholds.” Walker suggested that “low doses of peripherally selective  $\kappa$ -opioid agonists may offer the promise of improved therapy for neuropathic pain in humans . . .” *See* page 514, right column.

Thus, Walker clearly does not teach systemic treatment of neuropathy with N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide or a derivative, solvate, salt or stereoisomer thereof. Since Walker does not teach each and every element of the present invention, the strict identity standard for anticipation under 35 U.S.C. § 102 is not met. Accordingly, it is respectfully submitted that this rejection may properly be withdrawn.

### **Rejection under 35 U.S.C. § 103**

Claims 14, 20-22 and 37-39 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Walker in view of Bajwa *et al.* (*Geriatrics* 2001, 56(12):18-24, “Bajwa”). The

Office acknowledges that Walker does not specifically teach the treatment of post-herpetic neuralgia with N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide hydrochloride. To cure this deficiency of Walker, the Office cites Bajwa, which allegedly teaches that post-herpetic neuralgia is a chronic neuropathic pain syndrome that occurs as a complication of shingles, most commonly in older persons, and that combination therapy including antiviral, antidepressant, corticosteroid, opioid, and topical agents provides the most effective analgesia for post-herpetic neuralgia. The Office asserts that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Walker with the teaching of Bajwa because Walker teaches that asimadoline is effective for the treatment of neuropathic pain, and Bajwa teaches that neuropathic pain is a symptom of post-herpetic neuralgia. Therefore, treating neuropathic pain with asimadoline would result in the treatment of post-herpetic neuralgia, and one of ordinary skill in the art at the time the invention was made would have been motivated to use asimadoline for the treatment of postherpetic neuralgia.

Applicant respectfully traverses this rejection for the reasons set forth below.

The examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, (Fed. Cir. 1993). Only if this burden is met does the burden of coming forward with rebuttal argument or evidence shift to the applicant. *Id.* at 1532. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988). To establish a *prima facie* case of obviousness a three-prong test must be met. First, the prior art must reference must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). Second, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1731 (2007). Third, there must be a reasonable expectation of success found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

The obviousness analysis under 35 U.S.C. § 103(a) requires the consideration of the scope and content of the prior art, the level of skill in the relevant art, and the differences between the

prior art and the claimed subject matter. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)). It is improper to combine references where the references teach away from their combination. MPEP § 2145.X.D.2; *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). A *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. MPEP § 2144.05.III; *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997) (emphasis added). The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. MPEP § 2145.X.D.3; *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986) (emphasis added).

Claim 14 as amended is directed to the systemic treatment of neuropathy with N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidin-1-yl)ethyl]-2,2-diphenylacetamide or a derivative, solvate, salt or stereoisomer thereof. As discussed above, Walker explicitly states that intravenous (i.e., systemic) administration of asimadoline did not produce a change in nociception. *See* pages 511-512, Section 3.3. This statement clearly teaches away from the systemic administration of asimadoline and related compounds for the treatment of neuropathic pain, and specifically teaches away from the systemic administration of asimadoline and related compounds for the treatment of neuropathic pain secondary to nerve injury. Given the statements in Walker teaching away from the systemic administration of asimadoline for the treatment of neuropathic pain secondary to nerve injury, systemic administration of asimadoline for the treatment of neuropathic pain would be considered contrary to accepted wisdom at the time of the invention. The law clearly states that proceeding contrary to accepted wisdom in the art is evidence of nonobviousness (*Hedges*).

It has recently been demonstrated that systemic administration of asimadoline is successful in reducing tactile allodynia in rats. *See* Granados-Soto *et al.*, “Effect of asimadoline and ICI-20448 on neuropathic pain in the rat.” Program No. 514.7, Society for Neuroscience, 2005 (attached as **Exhibit A**). This animal study induced peripheral neuropathy by ligation of a spinal nerve. Neuropathy was confirmed by the presence of tactile allodynia. Subcutaneous administration of asimadoline dose-dependently reduced tactile allodynia. This effect was partially reduced by subcutaneous, but not intrathecal, naloxone. Intrathecal administration of asimadoline also reduced

tactile allodynia in a dose-dependent manner and this effect was completely blocked by intrathecal naloxone. These results indicate that systemic and intrathecal injection of asimadoline reduces tactile allodynia. This publication provides further evidence that systemic administration of asimadoline is useful as a treatment of neuropathic pain secondary to nerve injury.

Furthermore, the use of asimadoline in CCI rats does not teach or suggest the use of asimadoline or related compounds in neuropathic pain associated with post-herpetic neuralgia. It is well-known in the art that different experimental animal models have relevance to different classes of clinical neuropathies. *See* Aley & Levine, “Different peripheral mechanisms mediate enhanced nociception in metabolic/toxic and traumatic painful peripheral neuropathies in the rat”, *Neuroscience* 2002, 2:389-397 (attached as **Exhibit B**). There appears to be a significant difference in mechanisms underlying pain in non-traumatic neuropathies compared to neuropathies occurring after direct nerve trauma, which indicates that “experimental studies employing the chronic constriction injury . . . model[ ] may have limited applicability to understanding mechanisms active at peripheral nociceptor terminals in non-traumatic neuropathies in humans.” *Id.*, page 395, right column (emphasis added). Therefore, the CCI-induced neuropathy model used in Walker does not provide any teaching or suggestion regarding testing the efficacy for asimadoline or related compounds *in vivo* (*i.e.* in post-herpetic neuralgia) and describes no experiments that could be used to test the effectiveness of asimadoline and related compounds for such conditions. Therefore, any assertion that the disclosure in Walker suggests that asimadoline could be useful for the treatment of post-herpetic neuralgia is unfounded and would be mere speculation.

In view of the amendments to the claims and the arguments set forth above, Walker and Bajwa, alone or in combination, fail to teach every element of the claimed invention and provide no motivation for combining or modifying the teachings of said references with a reasonable expectation of success to arrive at the claimed invention. Accordingly, Applicant respectfully submits that this rejection under 35 U.S.C. § 103(a) may properly be withdrawn.

**CONCLUSION**

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing **docket no. 613242000900**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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